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GROWTH HORMONE EXCESS IN DOGS

Summary

Growth hormone (GH) related disorders include acromegaly and pituitary dwarfism. The pathogenesis of acromegaly is quite different in dogs and cats. In cats, a pituitary somatotroph adenoma that secretes excessive amounts of GH is the cause of acromegaly. However, in middle-aged and elderly female dogs, either endogenous progesterone (luteal phase of the estrous cycle) or exogenous progestins (used for estrus prevention) may give rise to GH hypersecretion of mammary origin. In addition, primary hypothyroidism is associated with elevated plasma concentrations of GH in dogs. In rare cases a pituitary somatotroph adenoma may also cause acromegaly in the dog.

Progesterone-induced acromegaly in dogs can be treated effectively by ovariectomy. Administration of progesterone receptor blockers has been shown to result in a significant decrease in plasma GH levels in dogs with progestin-induced acromegaly. Treatment of dogs with primary hypothyroidism with levo-thyroxine results in normalization of plasma GH levels. In dogs and cats with acromegaly due to a somatotroph adenoma, treatment should be directed at the pituitary lesion. Hypophysectomy is the treatment of choice.

Introduction

Like the other hormones of the pituitary anterior lobe, growth hormone (GH) is secreted in rhythmic pulses and intervening troughs. Pituitary GH secretion is regulated mainly by the opposing actions of the stimulatory hypothalamic peptide GH-releasing hormone (GHRH) and the inhibitory hypothalamic peptide somatostatin. The GH pulses predominantly reflect the pulsatile delivery of GHRH, whereas GH levels between pulses are primarily under somatostatin control. GH release can also be elicited by synthetic GH secretagogues. These GH secretagogues exert their effect on GH release by acting through receptors different from those for GHRH. In 1999, Kojima et al characterized the endogenous ligand for these receptors and called it ghrelin. The main source of circulating ghrelin appears to be the stomach. Ghrelin is a potent stimulator of pituitary GH release and in young dogs it is even a more potent GH secretagogue than GHRH (Bhatti et al. 2002). The main function of ghrelin, however, is in meal initiation. Fasting and food intake are associated with higher and lower circulating ghrelin concentrations, respectively (Bhatti et al. 2006a). Besides stimulating food intake ghrelin also stimulates gastric and intestinal emptying.

In the dog, circulating GH not only originates from the pituitary but also may be of mammary origin. In the 1970s and 1980s it was shown that administration of progestins could lead to elevated plasma GH levels in dogs. These progestin-stimulated plasma GH levels do not have a pulsatile secretion pattern, are not sensitive to stimula¬tion with GHRH, and are not inhi¬bi¬ted by somatostatin. Moreover, the progestin-induced elevated plasma GH levels do not decrease after hypophysectomy, indicating that this GH originates from an extrapituitary site. In 1994, Selman et al. published that the progestin-induced GH production in the dog originates from foci of hyperplastic ductular epithelium of the mammary gland. It was also demonstrated that mammary GH is biochemically identical to pituitary GH and that the gene encoding GH in the mammary gland is identical to the gene in the pituitary gland (Mol et al. 1995).

The pulsatile secretion pattern of GH also changes during progression of the luteal phase of healthy bitches, with higher basal GH secretion and less GH secreted in pulses during stages with a high plasma progesterone concentration (Kooistra et al. 2000). This may be explained by partial suppression of pituitary GH release by progesterone-induced GH production in the mammary gland. This indicates that progestin-induced mammary GH production is not just an aberration, but a normal physiological event during the luteal phase of the estrous cycle in healthy cyclic bitches. The GH receptor is also present in the mammary gland, which supports the concept that the progesterone-induced mammary GH production may promote the physiological proliferation of mammary gland tissue and the preparation for lactation during the luteal phase by local autocrine and paracrine effects. The progestin-induced mammary GH production may also play a role in mammary gland tumor development or tumor progression.

The effects of circulating GH can be divided into two main categories: rapid catabolic actions and slow (long-lasting) hypertrophic actions. The acute catabolic actions are mainly due to insulin antagonism and result in enhanced lipolysis, gluconeogenesis, and restricted glucose transport across the cell membrane. The net effect of these catabolic actions is promotion of hyperglycemia. The slow anabolic effects are mainly

mediated via insulin-like growth factors (IGFs). IGFs are produced in many different tissues, and in most of these tissues they have a local (paracrine or autocrine) growth-promoting effect. The main sources of circulating IGF-I are the liver and kidneys. The chemical structure of IGFs has about 50% sequence similarity with insulin. In contrast to insulin, IGFs are bound to binding proteins (IGFBPs). As a result of this binding to carrier proteins they have a prolonged half-life, which is consistent with their long-term growth-promoting actions. IGFs are important determinants in the regulation of body size, by stimulating protein synthesis, chondrogenesis, and growth.

The separation of the two opposing biologic effects of GH is not as strict as indicated in the previous paragraph. There is increasing evidence that GH exerts its growth-promoting effect not only via IGFs but also by a direct effect on the cells. Furthermore, there is now evidence that not so much IGF-I but rather GH may be the major determinant of body size. It appears that young dogs of large breeds go through a longer period of high GH release (i.e., juvenile hypersomatotropism) than young dogs of small breeds (Favier et al. 2001). On the other hand, there is a strong linear correlation between plasma IGF-I concentrations and body size. Furthermore, a single IGF-I single-nucleotide polymorphism haplotype has been reported as an important factor in determining final body size of dogs (Sutter et al. 20067.

IGF-I exerts an inhibitory effect on GH release, by stimulating the release of somatostatin and by a direct inhibitory influence at the pituitary level. In addition, GH itself has a negative feedback effect at the hypothalamic level.

ACROMEGALY

Pathogenesis

Acromegaly is a syndrome of bony and soft tissue overgrowth and insulin resistance due to excessive GH secretion. The pathogenesis of acromegaly is quite different in dogs and cats. In middle-aged and elderly female dogs, either endogenous progesterone (luteal phase of the estrous cycle) or exogenous progestins (used for estrus prevention) may give rise to GH hypersecretion of mammary origin. In addition, primary hypothyroidism is associated with elevated plasma concentrations of GH and IGF-I in dogs (Diaz-Espineira et al. 2008). Finally, in rare cases a pituitary somatotroph adenoma may cause acromegaly in the dog (Fracassi et al. 2007).

In cats, a pituitary somatotroph adenoma that secretes excessive amounts of GH is the cause of acromegaly. The condition is encountered most often in middle-aged and elderly, predominantly male, cats. Progestins may also induce GH expression in mammary tissue in the cat, but in this species the hormone does not seem to reach the systemic circulation.

Clinical manifestations

Signs and symptoms of GH hypersecretion tend to develop slowly and are characterized initially (particularly in the dog) by soft tissue swelling of the face and the abdomen. In some acromegalic dogs severe hypertrophy of soft tissues of the mouth, tongue, and pharynx causes snoring and even dyspnea. Dogs are presented often with polyuria (and sometimes polyphagia). The polyuria is usually without glucosuria, but manifest diabetes mellitus can develop due to insulin resistance. Physical examination may reveal thick skin folds, especially in the neck, prognathism and wide interdental spaces. Prolonged GH excess also leads to generalized visceromegaly resulting in abdominal enlargement. Laboratory investigations in acromegalic dogs will often reveal hyperglycemia and elevated plasma levels of alkaline phosphatase. The latter may, in part, be due to the intrinsic glucocorticoid activity of progestins.

The physical changes in cats tend to be less pronounced than in dogs. The head may become somewhat massive and may have rather pronounced features. The most common reason why cats with acromegaly are presented is because of (insulin-resistant) diabetes mellitus. Especially cats requiring lente insulin dosages > 1.5 IU/kg body weight per injection should be screened for acromegaly (Slingerland et al. 2008). Recent studies suggest that approximately 15% of cats with diabetes mellitus have acromegaly, indicating that cats with diabetes mellitus should be screened for the presence of acromegaly (Berg et al. 2007; Niessen et al. 2007). In a minority of cases, acromegalic cats may have proliferative changes affecting the joints leading to a progressive degenerative arthropathy with lameness. Affected cats may have dyspnea due to hypertrophic cardiomyopathy. The pituitary adenoma causing acromegaly may become rather large in cats and may therefore result in neurological signs. For many

acromegalic cats the only routine laboratory changes are related to the secondary diabetes mellitus in the form of hyperglycemia and glucosuria. Sometimes feline acromegaly co-exists with pituitary-dependent hypercortisolism (Meij et al. 2004).

Diagnosis

The basal plasma GH level in acromegalic animals often exceeds the upper limit of the reference range (5 µg/L in dogs and 7.2 µg/L in cats). However, if the disease is mild or just beginning, the basal plasma GH levels may be only slightly elevated. Conversely, a high value may be the result of a secretory pulse in a normal subject. Nonresponsiveness of normal or elevated GH levels to stimulation may further support the diagnosis. Because of the variation in amino acid sequence of GH in different species, GH levels should be determined by a species-specific, homologous radioimmunoassay. Feline GH can be measured reliably in a radioimmunoassay developed for the dog.

Assays for measuring GH are not widely available. Being bound to proteins, the IGF-I level is much less subject to fluctuation than that of GH. In addition, the amino acid sequence of IGF-I is less species specific than that of GH and therefore IGF-I can be determined in a heterologous (human) assay. This has led to the use of IGF-I measurements as diagnostic tests for acromegaly in cats (Berg et al. 2007). However, there is some overlap in plasma IGF-I levels between healthy animals and individuals with acromegaly. Furthermore, plasma IGF-I concentrations may be low in untreated and short-term treated diabetic cats, whereas they increase during treatment with insulin (Reusch et al. 2006; Alt et al. 2007). This may lead to non-elevated plasma IGF-I concentrations in untreated diabetic cats with acromegaly. When such cats are treated with insulin, plasma IGF-I concentrations may rise considerably.

The pituitary tumors causing hypersecretion of GH tend to be large in cats. Consequently, when acromegaly has been demonstrated in a cat, the pituitary should be visualized by computed tomography (CT) or magnetic resonance imaging (MRI).

Treatment

Progesterone-induced acromegaly in dogs can be treated effectively by ovario(hyster) ectomy. In cases in which the GH excess did not lead to complete exhaustion of the pancreatic β-cells, elimination of the progesterone source by ovario(hyster)ectomy may prevent persistent diabetes mellitus. Dogs with progestin-induced GH excess should not be treated anymore with progestins. Administration of progesterone receptor blockers such as aglépristone has been shown to result in a significant decrease in plasma levels of GH and IGF-I in dogs with progestin-induced acromegaly (Bhatti et al. 2006b). Treatment of dogs with primary hypothyroidism with levo-thyroxine results in normalization of plasma levels of GH and IGF-I (Diaz-Espineira et al. 2008).

In dogs and cats with acromegaly due to a somatotroph adenoma, treatment should be directed at the pituitary lesion. In principle, there are three options: medical treatment, radiation therapy, and hypophysectomy. Medical treatment with (expensive) long-acting somatostatin analogues, such as octreotide and lanreotide, improve symptoms of acromegaly in most human acromegalic patients, with normalization of plasma levels of IGF-I and tumor shrinkage occurring in approximately 50% of cases. Also in cats it has been shown that some acromegalic cats respond to administration of a somatostatin analogue with a pronounced decrease in plasma GH concentrations (Slingerland et al. 2008, Scudder et al. 2015), suggesting that in these cats long-acting somatostatin analogues may be useful. The development of GH-receptor antagonists such as pegvisomant in human medicine may also hold promises for dogs and cats with acromegaly. Radiation therapy shrinks the pituitary tumor and may improve diabetic control in acromegalic cats (Mayer et al. 2006). Disadvantages of radiation therapy include limited availability, extended hospitalization, frequent anesthesia, high expense, and the possibility of relapse. Transsphenoidal hypophysectomy has been performed successfully in dogs and cats with hypercortisolism due to a corticotroph adenoma (Meij et al. 1998, Meij et al. 2001) and is also an effective treatment option for animals with a somatotroph adenoma (Meij et al. 2010).

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Further reading

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